REMARKS

Upon entry of the above amendment, claims 1, 2, 4-6, 10, 11, 25-28 and 31 will be pending, claims 3, 13, 17-19 and 30 having been cancelled. Claim 1 has been amended to specify a mammalian transporter. Claims 12 and 16 have been amended to incorporate the limitations of claim 6 and are designated as "Withdrawn-Currently amended" as they drawn to methods that correspond to non-elected Groups II and III, respectively. Dependent claims that depend from claim 12, that is, claims 14, 15 and 29; and dependent claims that depend from claim 16, that is claims 20-24, have been designated as "Withdrawn." Support for amended claims can be found in the specification and in the original claims as filed. Support for amended claim 1 can be found, for example, in the specification at page 1, lines 16-19; in Examples 1, 2 and 3 and in claim 3 as originally filed. Support for amended claim 12 can be found, for example, in claim 12 as originally filed and in Examples 1, 2, and 3. Support for amended claim 16 can be found, for example, in the specification at page 14, lines 1-21 and in claim 16 as originally filed. No new matter has been added. Applicant intends to seek rejoinder of Groups II and III upon allowance of elected claims.

Interview Summary

Applicant thanks the Examiner for the Interview Summary of March 6, 2008 in which it was noted that the shortened statutory period for reply entered in the Office Action has been corrected.

Election/Restrictions

The Examiner made final the restriction of Groups II and III and removed claims 12-24 from further consideration. Applicant continues to disagree with the Examiner regarding Garcia (*Journal of Biological Chemistry* 270: 1843-1849 (1995)) for reasons of record. Without conceding that claims 12-24 as presented fail to satisfy any statutory requirements, Applicant elects Group I in order to expedite prosecution. Applicant intends to seek rejoinder of the non-elected claims which have been amended to include the limitations of the elected invention.

35 U.S.C. § 103(a)

The Examiner rejected claims 1-6, 10-11, 25-28 and 31 as obvious over Miyasaka *et al.*, (*Protein Expression and Purification*, 23: 389-397 (2001)) in view of Loisel *et al.*, (*Nature Biotechnology*, 15: 1300-1304 (1997)) and Hsu *et al.* (*Pharmaceutical Research*, 15: 1376-1380 (1998)). According to the Office Action at page 6:

> [I]t would be obvious for one skilled in the art to modify the method for expressing an adrenergic receptor, wherein the method comprises culturing a host infected cell with a recombinant virus that comprises a gene encoding the receptor, expressing the transporter on the envelope of a budding virus released from the host as taught by the peptide taurine transporter of Miyasaka *et al.*, and using the transporter, PepT1, as taught by Hsu *et al.* (1996). One of ordinary skill in the art at the time the invention was made would been motivated to express Pept1 in baculovirus because extracellular virions (ECV) of baculovirus may be used to study plasma-membrane restricted processes (Loisel *et al.*, page 1303, right column, 1st paragraph). One skilled in the art would have expected success because the PepT1 gene has been expressed successfully in a viral vector and numerous other membrane transporters have already been expressed in Sf9 cells using the baculovirus system at the time the invention was made. Accordingly, the invention taken as a whole is prima facie obvious.

Applicant respectfully traverses with respect to the claims as currently amended for the following reasons. Loisel discloses a method of expressing the β_2Adrenergic Receptor (β_2AR) on baculoviral particles. However, one of skill in the art would not read Loisel and conclude that his method would be generally applicable to expression of transport proteins on baculoviral particles. Loisel's objective was to express mammalian β_2AR in a heterologous system for structural studies. As Loisel notes, others had found that infection of insect Sf9 cells with the HIV protein Pr55Gag resulted in the release of virus-like particles (Gag particles) and that host cell plasma membrane proteins could be found in these particles. When Loisel tried to obtain mature GPCR in budding Gag particles by coinfected Sf9 cells with two baculoviruses, one expressing a GPCR and the other expressing HIV-1 Pr55 Gag, he was unsuccessful. He states: "Unexpectedly, most of the recombinant adrenergic receptor was excluded from the Gag-particles and was found instead to be associated with extracellular virions (ECV) of baculovirus"(at page 1300, col. 1, para. 2). If obtaining viral particles expressing a transmembrane protein were simply a matter of expressing a transmembrane protein on the

plasma membrane of an infected cell, a person of ordinary skill might well have expected Loisel to have been more successful in their initial objective of expressing β_2AR on budding Gag particles.

Loisel suggests that it was not the plasma membrane localization of β_2AR that permitted inclusion on viral particles, but rather association with the nucleus:

> Although it could not be excluded that molecules of β_2AR could be inserted in the plasma membrane and then become part of the baculovirus envelope, our results suggest that a proportion of the ECV-associated β_2AR originated from the intranuclear pool of β_2AR molecules where they interact with the baculovirus nucleocapsids. The origin of the nuclear β_2AR remains unclear. The nuclear envelope and the rough endoplasmic reticulum are functionally equivalent and the nuclear membrane may be the source of nuclear glycoproteins synthesized upon baculovirus infection [citations omitted]. In addition, synthesis of GPCR within the nuclear membrane has previously been suggested. (at page 1302, col. 1, para. 1) (Emphasis added.)

It was well known in the art at the time the application was filed that transporters are synthesized on the cytoplasmic endoplasmic reticulum and are transported through the Golgi network to the cell surface. For example, Miyakasa mentions this pathway in reference to "the amount of taurine transporter that leaves the endoplasmic reticulum as functional transporter for Golgi layers and is ultimately inserted in the plasma membrane." (Page 395, right column, lines 18-22.)

Loisel does not disclose or suggest a protein that is synthesized on the cytoplasmic endoplasmic reticulum and transported through the Golgi network to the cell surface. Loisel discloses instead that the β_2AR protein was found associated with budding baculovirus, intranuclear baculoviruses and in nuclear inclusions (at page 1302, col. 1, para. 1; see also Figure 3D.) One of skill in the art would have no reason to believe that a transporter protein would be synthesized in or localized to the nucleus.

Miyakasa is cited for its disclosure of "a method of culturing Sf9 cells with the recombinant virus baculovirus that comprises the taurine transporter gene... and harvesting the released virus from plated Sf9 cells." (Office action at page 5.) The Office Action appears to be confusing the steps that Miyakasa took to produce the viral strains they used for the infection of Sf9 cells with the steps of the claimed methods which recite harvesting a released virus that has a transporter on the viral envelope that has transporter activity. Applicant reiterates that Miyasaka

et al., teach methods for expressing recombinant taurine transporter in insect cells in order to study transporter activity in cells, not on the envelopes of virus released from the cells. Miyasaka *et al.*, do not teach or suggest a step of harvesting or otherwise purifying a budding virus from the infected cells, and provide no reason one might want to do so.

Nor does Hsu make up for what is lacking in either Miyakasa or Loisel. Hsu is cited for its disclosure of a recombinant adenovirus encoding PepT1. The disclosure of an adenoviral vector for expression of PepT1 in mammalian cell lines would simply not prompt one of skill in the art to prepare a budding baculovirus expressing a PepT1 transporter having PepT1 transporter activity. Adenoviruses and baculoviruses belong to different genera entirely and are in no way interchangeable; the former infects only mammalian cells, the latter only insect cells. Hsu's objective was to set up a mammalian cell-based screen for peptide drugs. The Applicant's specification makes clear that the budding baculovirus system of the claims was developed in part because mammalian cell-based screens tend to have relatively high background levels of transporter activity due to expression of endogenous transporter proteins (specification at page 2, lines 2-5). The fact that the PepT1 gene "has been expressed successfully in a viral vector" (Office Action at page 6) would not provide one of skill in the art with the expectation that the invention would work, *i.e.*, that the viral envelope of a budding virus such as a baculovirus could be made to express a transporter having transporter activity. Nor would the "numerous other membrane transporters [have] already [been] expressed in Sf9 cells" (Office Action at page 6) provide an expectation of success. If the Examiner believes there are "numerous other references" that would do so, Applicant respectfully requests that the Examiner identify the references and explain where the limitation of the claims are found in each references so that the Applicant can understand and directly address his reasoning.

For at least these reasons, Applicant submits that the Examiner has not made out a prima facie case of obviousness, and request that the obviousness rejection be withdrawn.

Please charge any required fees and apply any other charges or credits to deposit account 06-1050 referencing attorney docket no. 14875-0133US1.

Respectfully submitted,

Date: March 5, 2009

Gretchen L. Temeles, PhD.
Reg. No. 57,077

Customer No.: 26161
Fish & Richardson P.C.
Telephone: (302) 652-5070
Facsimile: (877) 769-7945